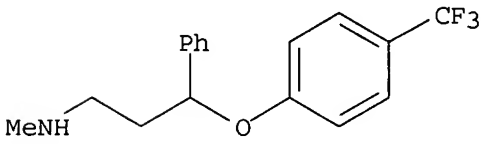
```
=> s fluoxetine/cn
L1            1 FLUOXETINE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   54910-89-3  REGISTRY
CN   Benzenepropanamine, N-methyl-.gamma.-[4-(trifluoromethyl)phenoxy]- (9CI)
     (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Benzenepropanamine, N-methyl-.gamma.-[4-(trifluoromethyl)phenoxy]-,
     (.+-.)-
OTHER NAMES:
CN   (.+-.)-Fluoxetine
CN   (.+-.)-N-Methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propylamine
CN   3-(p-Trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine
CN   Deprex
CN   dl-3-(p-Trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine
CN   Fluoxetine
CN   Fluval
DR   57226-07-0, 52341-67-0
MF   C17 H18 F3 N O
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT,
       CBNB, CEN, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, CSNB, DDFU, DIOGENES,
       DRUGNL, DRUGPAT, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA,
       MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*,
       SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
         (*File contains numerically searchable property data)
     Other Sources:   WHO
```

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**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

           2325 REFERENCES IN FILE CA (1962 TO DATE)
             22 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
           2331 REFERENCES IN FILE CAPLUS (1962 TO DATE)
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(FILE 'HOME' ENTERED AT 15:58:32 ON 17 DEC 2002)

FILE 'REGISTRY' ENTERED AT 15:58:43 ON 17 DEC 2002

L1 1 S FLUOXETINE/CN

FILE 'CA, CABA, CAPLUS, MRCK, DRUGU, IFIPAT, DRUGPAT, USPATFULL' ENTERED AT 15:59:33 ON 17 DEC 2002

L2 7693 S L1
L3 2219407 S COATINGS OR LAYERS OR SEPATATING OR ENTERIC
L4 2804922 S COATINGS OR LAYERS OR SEPARATING OR ENTERIC
L5 229 S L4 AND L2
L6 206 S L5 AND HPMCAS OR HYDROXYPROPYLMETHYL CELLULOSE ACETATE SUCCI
L7 30 S L6 AND PELLETS
L8 2001913 S L6 AND PELLETS OR PARTICLES OR GRANULES
L9 2147753 S PELLETS OR PARTICLES OR GRANULES
L10 144 S L6 AND L9
L11 8 S L10 AND PINDOLOL

L11 ANSWER 1 OF 8 USPATFULL
ACCESSION NUMBER: 1999:146022 USPATFULL
TITLE: Method for the treatment of CNS disorders
INVENTOR(S): Anderson, Neil R., West Lafayette, IN, United States
Harrison, Roger F., Zionsville, IN, United States
Lynch, Daniel F., Indianapolis, IN, United States
Oren, Peter L., Fishers, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5985322		19991116
APPLICATION INFO.:	US 1999-265610		19990310 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-867196, filed on 29 May 1997, now patented, Pat. No. US 5910319
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Seidleck, Brian K.
LEGAL REPRESENTATIVE: Titus, Robert D., Conrad, Robert A.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 783
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improved method for the treatment of central nervous system disorders comprises treating patients with an **enteric** fluoxetine formulation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An improved method for the treatment of central nervous system disorders comprises treating patients with an **enteric** fluoxetine formulation.
SUMM This invention belongs to the field of pharmaceutical science, and provides a superior **enteric** formulation of the anti-depressant drug, fluoxetine.
SUMM **Enteric** pharmaceutical formulations are manufactured in such a way that the product passes unchanged through the stomach of the patient, and. . . ingredient is in the inner part of the tablet or pellet and is enclosed in a film or envelope, the "**enteric** coating", which is insoluble in acid environments, such as the stomach, but is soluble in near-neutral environments such as the. . .
SUMM Certain difficulties arose in preparing conventional **enteric** formulations of fluoxetine. In particular, fluoxetine was found to react with many **enteric coatings** to form a slowly- or even insoluble coating. Similar reactions with **enteric coatings** have been observed with other drugs--duloxetine, nortriptyline, desipramine, sertraline and paroxetine.
SUMM Duloxetine, undergoing clinical evaluation as a candidate antidepressant, is (+)-N-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine, and is commonly used as its hydrochloride salt. An **enteric** coated formulation of duloxetine is claimed in U.S. Pat. No. 5,508,276, to avoid acid degradation of the compound in the. . .
SUMM The present invention was created through efforts to solve the above and other problems, and provides a superior **enteric** formulation of fluoxetine.
SUMM The present invention provides an **enteric** fluoxetine pellet comprising a) a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropyl-methylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer.

SUMM The invention also provides a method of manufacturing an **enteric** fluoxetine pellet comprising a) providing a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) optionally, applying to the core a **separating** layer comprising one or more pharmaceutically acceptable excipients; c) applying an **enteric** layer comprising **HPMCAS** and one or more pharmaceutically acceptable excipients, wherein the **HPMCAS** is applied as an aqueous solution or suspension and the application takes place in an apparatus of the fluid bed. . .

SUMM . . . of percentage, ratio, proportion and the like, will be in weight units unless otherwise stated. Expressions of proportions of the **enteric** product will refer to the product in dried form, after the removal of the water in which many of the. . .

SUMM The various components and **layers** of the pellet will be individually discussed as follows, together with the methods of adding the different ingredients to build. . .

SUMM The size of the cores depends, of course, on the desired size of the pellet to be manufactured. In general, **pellets** can be as small as 0.1 mm, or as large as 2 mm. Preferred cores are from about 0.3 to about 0.8 mm, in order to provide finished **pellets** in the desired preferred size range of from about 0.5 to about 1.5 mm in diameter.

SUMM . . . the cores to be of a reasonably narrow particle size distribution, in order to improve the uniformity of the various **coatings** to be added and the homogeneity of the final product. For example, the cores may be specified as being of. . .

SUMM The amount of cores to be used obviously depends on the weights and thicknesses of the added **layers**; in general, the cores comprise from about 10 to about 70 percent of the product. More preferably, the charge of. . .

SUMM . . . in general. The amount of fluoxetine, of course, depends on the desired dose of the drug and the quantity of **pellets** which it is desired to administer. The dose of fluoxetine is in the range of 20-100 mg (base equivalent), more usually 80-90 mg, and the usual amount of **pellets** is that amount which is conveniently held in gelatin capsules. Comparison of the volume of gelatin capsules and the desired. . .

SUMM . . . conducted in conventional coating pans similar to those employed in sugar coating processes. This process can be used to prepare **pellets**, but this equipment has less efficient air flow and drying capabilities which limits application rates and can result in longer. . .

SUMM . . . plate equipment typically consists of a cylinder, the bottom of which is a rotatable plate. Motion of the mass of **particles** to be coated is provided by friction of the mass between the stationary wall of the cylinder and the rotating. . .

SUMM When a powder coating is to be applied, the mass of **pellets**, in the present case, is maintained in a sticky state, and the powder to be adhered to them, fluoxetine in this case, is added continuously or periodically and adheres to the sticky **pellets**. When all of the fluoxetine has been applied, the spray is stopped and the mass is allowed to dry in. . .

SUMM . . . spraying nozzle close above the bottom, or a downward-spraying nozzle mounted above the product mass. The cylinder is charged with **particles** to be coated, sufficient volume of air is drawn through the bottom of the cylinder to suspend the mass of **particles**, and the liquid to be applied is sprayed onto the mass. The temperature of the fluidizing air is balanced against the spray rate to maintain the mass of **pellets** or tablets at the desired level of moisture and stickiness while the coating is built up.

SUMM . . . a mass of pharmaceutical excipients, moistening the mass with water or a solvent, drying, and breaking the mass into sized **particles** in the same size range as described above for the

inert cores. This can be accomplished via the process of. . .

SUMM **Separating** Layer

SUMM The **separating** layer between the fluoxetine-containing core and the **enteric** layer is not required, but is a preferred feature of the formulation. The functions of the **separating** layer, if required, are to provide a smooth base for the application of the **enteric** layer, to prolong the pellet's resistance to acid conditions, and to improve stability by inhibiting any interaction between the drug and the **enteric** polymer in the **enteric** layer.

SUMM The smoothing function of the **separating** layer is purely mechanical, the objective of which is to improve the coverage of the **enteric** layer and to avoid thin spots in it, caused by bumps and irregularities on the core. Accordingly, the more smooth and free of irregularities the core can be made, the less material is needed in the **separating** layer, and the need for the smoothing characteristic of the **separating** layer may be avoided entirely when the fluoxetine is of extremely fine particle size and the core is made as. . .

SUMM It has been found that, when a pharmaceutically acceptable non-reducing sugar is added to the **separating** layer, the pellet's resistance to acid conditions is markedly and surprisingly increased. Accordingly, such a sugar may be included in the **separating** layer applied to the cores, either as a powdered mixture, or dissolved as part of the sprayed-on liquid. A sugar-containing **separating** layer can reduce the quantity of **enteric** polymer required to obtain a given level of acid resistance. It therefore considerably reduces the expense of the present formulated product. Use of less **enteric** polymer reduces both the materials cost and processing time, and also reduces the amount of polymer available to react with fluoxetine. The inhibition of any core/**enteric** layer interaction is mechanical. The **separating** layer physically keeps the components in the core and **enteric layers** from coming into direct contact with each other. In some cases, the **separating** layer can also act as a diffusional barrier to migrating core or **enteric** layer components dissolved in product moisture. The **separating** layer can also be used as a light barrier by opacifying it with agents such as titanium dioxide, iron oxides. . .

SUMM In general, the **separating** layer is composed of coherent or polymeric materials, and finely powdered solid excipients which constitute fillers. When a sugar is used in the **separating** layer, it is applied in the form of an aqueous solution and constitutes part of or the whole of the coherent material which sticks the **separating** layer together. In addition to or instead of the sugar, a polymeric material may also be used in the **separating** layer. For example, substances such as hydroxypropylmethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like may be used in small amounts to increase the adherence and coherence of the **separating** layer.

SUMM It is further advisable to use a filler excipient in the **separating** layer to increase the smoothness and solidity of the layer. Substances such as finely powdered talc, silicon dioxide and the. . . universally accepted as pharmaceutical excipients and may be added as is convenient in the circumstances to fill and smooth the **separating** layer.

SUMM In general, the amount of sugar in the **separating** layer may be in the range of from about 2% to about 10% of the product, when a sugar is. . .

SUMM The **separating** layer may be applied by spraying aqueous solutions of the sugar or polymeric material, and dusting in the filler as has been described in the preparation of a fluoxetine layer. The smoothness and homogeneity of the **separating** layer can be

improved, however, if the filler is thoroughly dispersed as a suspension in the solution of sugar and/or. . . suspension is sprayed on the core and dried, using equipment as described above in the preparation of cores with fluoxetine **layers**.

SUMM **Enteric** Layer

SUMM The **enteric** layer is comprised of an **enteric** polymer, which must be chosen for compatibility with fluoxetine as discussed above. The polymer must be one having only a small number of carboxylic acid groups per unit weight or repeating unit of the polymer. The preferred **enteric** polymer is hydroxypropylmethylcellulose acetate succinate (**HPMCAS**), which product is defined as containing not less than 4% and not more than 28% of succinoyl groups, which are. . . the only free carboxylic groups in the compound. See Japanese Standards of Pharmaceutical Ingredients 1991, page 1216-21, Standard No. 19026. **HPMCAS** is available from Shin-Etsu Chemical Co., Ltd., Tokyo, Japan, under the trademark AQOAT. It is available in two particle size. . .

SUMM **Enteric** polymers may be applied as **coatings** from aqueous suspensions, from solutions in aqueous or organic solvents, or as a powder. Application from organic solvents is presently. . . difficulty in either disposing of solvent vapors or recovering the evaporated solvent. Accordingly, no detailed discussion of application of the **enteric** layer from organic solvents will be given here, but the pharmaceutical scientist will recognize that such application is entirely possible. . .

SUMM The **enteric** polymer can also be applied according to a method described by Shin-Etsu Chemical Co. Ltd. (Obara, et al., Poster PT6115, AAPS Annual Meeting, Seattle, Wash., Oct. 27-31, 1996). When the **enteric** polymer is applied as a powder the **enteric** polymer is added directly in the solid state to the tablets or **pellets** while plasticizer is sprayed onto the tablets or **pellets** simultaneously. The deposit of solid **enteric particles** is then turned into a film by curing. The curing is done by spraying the coated tablets or **pellets** with a small amount of water and then heating the tablets or **pellets** for a short time. This method of **enteric** coating application can be performed employing the same type of equipment as described above in the preparation of cores with fluoxetine **layers**

SUMM When the **enteric** polymer is applied as an aqueous suspension, a problem in obtaining a uniform, coherent film often results. It is very advisable, accordingly, to purchase a fine particle grade or grind the **particles** of polymer to an extremely small size before application. It is possible either to grind the dry polymer, as in. . . form. Slurry grinding is generally preferable, particularly since it can be used also to grind the filler portion of the **enteric** layer in the same step. It is advisable to reduce the average particle size of the **enteric** polymer to the range from about 1 .mu.m to about 5 .mu.m, preferably no larger than 3 .mu.m.

SUMM When the **enteric** polymer is applied in the form of a suspension, it is important to assure that the suspension remains homogeneous, and. . . taken to assure that the suspension is kept moving briskly through the equipment to cool the tubing and nozzle. When **HPMCAS** is used, in particular, it is advisable to cool the suspension below 20.degree. C. before application, to cool the tubing. . .

SUMM It is preferred in the present invention, however, to apply the **enteric** polymer as an aqueous solution whenever it is possible to do so. In the case of **HPMCAS**, dissolution of the polymer can be obtained by neutralizing the polymer, preferably with ammonia. Neutralization of the polymer may be. . . the polymer when such a process is to be used. Use of neutralized polymer more readily provides a smooth, coherent **enteric** layer than when a suspended polymer is used, and use of partially neutralized polymer provides intermediate

degrees of smoothness and coherency. Particularly when the **enteric** layer is applied over a very smooth **separating** layer, excellent results may be obtained from partially neutralized **enteric** polymer.

SUMM . . . Still another preferred manner of neutralization is from about 25% to about 65% neutralized. It is found, however, that the **enteric** polymer in the resulting product, after drying, is neutralized to a lesser extent than when applied. When neutralized or partially neutralized **HPMCAS** is applied, the **HPMCAS** in the final product is from about 0% to about 25% neutralized, more preferably from about 0% to about 15%. . .

SUMM Most **enteric** polymers require the addition of a plasticizer for best results. In the case of **HPMCAS**, the preferred plasticizer is triethyl citrate, used in an amount up to about 15-30% of the amount of **enteric** polymer in aqueous suspension application. When a neutralized **HPMCAS** is employed, lower levels or no plasticizer may be required.

SUMM Usually, an **enteric** layer is filled with a powdered excipient such as talc, glyceryl monostearate or hydrated silicon dioxide to build up the. . . solids in the range of from about 1% to about 10% of the final product may be added to the **enteric** polymer mixture, while the amount of **enteric** polymer itself is usually in the range from about 5% to about 25%, more preferably, from about 10% to about. . .

SUMM Application of the **enteric** layer to the **pellets** follows the same general procedure previously discussed, using fluid bed type equipment with simultaneous spraying of **enteric** polymer solution or suspension and warm air drying. Temperature of the drying air and the temperature of the circulating mass of **pellets** should be kept in the ranges advised by the manufacturer of the **enteric** polymer.

SUMM A finishing layer over the **enteric** layer is not necessary in every case, but frequently improves the elegance of the product and its handling, storage and. . . less than 1% of an anti-static ingredient such as talc or silicon dioxide, simply dusted on the surface of the **pellets**. Another simple finishing layer is a small amount, about 1%, of a wax such as beeswax melted onto the circulating mass of **pellets** to further smooth the **pellets**, reduce static charge, prevent any tendency for **pellets** to stick together, and increase the hydrophobicity of the surface.

SUMM More complex finishing **layers** may constitute a final sprayed-on layer of ingredients. For example, a thin layer of polymeric material such as hydroxypropylmethylcellulose, polyvinylpyrrolidone. . . color agent such as red or yellow iron oxide. Such a layer quickly dissolves away in the stomach, leaving the **enteric** layer to protect the fluoxetine, but provides an added measure of pharmaceutical elegance and protection from mechanical damage to the. . .

SUMM Finishing **layers** to be applied to the present product are of essentially the same types commonly used in pharmaceutical science to smooth, seal and color **enteric** products, and may be formulated and applied in the usual manners.

SUMM The following Examples set out the preparation of a number of different **enteric granules** within the concept of the present invention. The Examples are intended further to enlighten the reader about the present **enteric pellets** and their methods of manufacture; additional variations within the concept of the invention will be clear to the pharmaceutical scientist. . .

SUMM . . . will be expressed in terms of the amount of each ingredient used to prepare a single unit dose of the **granules**. Following the bill of materials, the process will be described, giving the equipment and the batch size used in the. . .

DETD

Bill of Materials

Cores
Sucrose - starch nonpareils, 30-35 mesh 134.15 mg
Fluoxetine layer
Fluoxetine 100.58 mg
Sucrose 25.72 mg
Hydroxypropylmethylcellulose 12.89 mg
Separating layer
Hydroxypropylmethylcellulose 9.45 mg
Sucrose 28.24 mg
Talc, 500 mesh 50.21 mg
Enteric layer
HPMCAS-LF 65.66 mg
Triethyl citrate 13.14 mg
Talc, 500 mesh 19.66 mg
Finishing Layer
Color mixture white (HPMC + titanium dioxide) 43.02 mg
HPMC 10.78 mg
Talc. . .
DETD . . . fitted with a Wurster column. Upon completing the application of the desired quantity of fluoxetine hydrochloride suspension, the fluoxetine core **pellets** were completely dried in the fluid bed dryer.
DETD The **separating** layer which consisted of talc 12% w/w, sucrose 6.75% w/w and hydroxypropyl methylcellulose 2.25% w/w was then applied as an aqueous suspension to the fluoxetine core **pellets**. Upon completing the application of the desired quantity of suspension, the **pellets** were completely dried in the fluid bed dryer.
DETD The **enteric** coating aqueous suspension consisted of hydroxypropyl methylcellulose acetate succinate type LF 6% w/w, talc 1.8% w/w, triethyl citrate 1.2% w/w which was fully neutralized by the addition of 0.47% w/w ammonium hydroxide. This **enteric** coating suspension was applied to the fluoxetine separation layer coated **pellets**. Upon completing the application of the desired quantity of **enteric** coating suspension, the **pellets** were completely dried in the fluid bed dryer and a small quantity of talc was added to reduce static charge.
DETD . . . 8% w/w and hydroxypropyl methylcellulose 2% w/w. Upon completing the application of the desired quantity of color coating suspension, the **pellets** were completely dried in the fluid bed dryer and a small quantity of talc was added to reduce static charge. The resulting **pellets** were assayed for fluoxetine content and filled into capsules to provide 90 mg of fluoxetine base.
DETD
Bill of Materials

Cores
Sucrose - starch nonpareils, 30-35 mesh 134.19 mg
Fluoxetine layer
Fluoxetine hydrochloride 100.62 mg
Sucrose 25.77 mg
Hydroxypropylmethylcellulose 12.89 mg
Separating layer
Hydroxypropylmethylcellulose 6.12 mg
Sucrose 18.27 mg
Talc, 500 mesh 32.49 mg

Enteric layer
HPMCAS-LF 74.89 mg
Triethyl citrate 14.96 mg
Talc, 500 mesh 21.77 mg
Finishing layer
Color mixture white (HPMC + titanium dioxide)
43.02 mg
HPMC 10.78 mg
Talc. . .
DETD

Bill of Materials

Cores
Sucrose - starch nonpareils, 30-35 mesh
121.01 mg
Fluoxetine layer
Fluoxetine hydrochloride 100.60 mg
Sucrose 25.75 mg
Hydroxypropylmethylcellulose
12.85 mg
Separating layer
Hydroxypropylmethylcellulose
9.48 mg
Sucrose 28.38 mg
Talc, 500 mesh 50.45 mg
Enteric layer
HPMCAS-LF 66.78 mg
Triethyl citrate 13.36 mg
Talc, 500 mesh 20.01 mg
Finishing layer
Color mixture white (HPMC + titanium dioxide)
44.30 mg
HPMC 11.09 mg
Talc. . .
DETD

Bill of Materials

Cores
Sucrose - starch nonpareils, 30-35 mesh
100-150 mg
Fluoxetine layer
Fluoxetine hydrochloride
100.5-100.8
mg
Sucrose 20-30 mg
Hydroxypropylmethylcellulose
10-15 mg
Separating layer
Hydroxypropylmethylcellulose
4-12 mg
Sucrose 15-35 mg
Talc, 500 mesh 25-60 mg
Enteric layer
HPMCAS-LF 60-90 mg
Triethyl citrate 10-20 mg
Talc, 500 mesh 15-25 mg
Finishing layer
Color mixture white (HPMC + titanium dioxide)
35-55 mg
HPMC 5-15 mg
Talc. . .
DETD **Pellets** made according to the above examples, and gelatin capsules filled with various batches of such **pellets**, have

been thoroughly tested in the manners usual in pharmaceutical science. Results of stability tests show that the **pellets** and capsules have sufficient storage stability to be distributed, marketed and used in the conventional pharmaceutical manner.

DETD Testing further shows that the **pellets** and capsules pass the conventional tests for **enteric** protection under conditions prevailing in the stomach. It has also been shown that the **pellets** release their load of fluoxetine acceptably quickly when exposed to conditions prevailing in the small intestine. Accordingly, the present invention has been demonstrated to solve the problems which previously were encountered in the formulation of other fluoxetine **pellets**.

DETD . . . only fluoxetine as an active ingredient, a combination product of fluoxetine, particularly as the hydrochloride salt, may be made with **pindolol** as described in European Patent Application Publication 687,472. These active ingredients are generally present in the amounts of approximately 60-120 mg of fluoxetine hydrochloride and 1 to 60 mg of **pindolol**.

CLM What is claimed is:

. . . stress, worry, anger, rejection sensitivity, and lack of mental or physical energy without an increase in nausea comprising administering an **enteric** fluoxetine pellet comprising a) a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) an optional seperating layer comprising a non-reducing sugar; c) an **enteric** layer comprising hydroypropylmethylcellulose acetate succinate (**HPMCAS**) and one or more pharmaceutically acceptable excipients; d) an optional finishing layer.

. . . a formulation containing the following: _____

Cores		
Sucrose - starch nonpareils, 30-35 mesh	100-150	mg
Fluoxetine layer		
Fluoxetine hydrochloride	100.5-100.8	mg
Sucrose	20-30	mg
Hydroxypropylmethylcellulose	10-15	mg
Separating layer		
Hydroxypropylmethylcellulose	4-12	mg
Sucrose	15-35	mg
Talc, 500 mesh	25-60	mg
Enteric layer		
HPMCAS-LF	60-90	mg
Triethyl citrate	10-20	mg
Talc, 500 mesh	15-25	mg
Finishing layer		
Color mixture white (HPMC + titanium dioxide)	35-55	mg
HPMC	5-15	mg
Talc. . .		

IT **54910-89-3**, Fluoxetine 56296-78-7, Fluoxetine hydrochloride (enteric fluoxetine pellets)

L11 ANSWER 2 OF 8 USPATFULL

ACCESSION NUMBER: 1999:117001 USPATFULL
TITLE: Potentiation of serotonin response
INVENTOR(S): Wong, David T, Idianapolis, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5958429		19990928	
	WO 9706792		19970227	
APPLICATION INFO.:	US 1998-11937		19980728	(9)
	WO 1996-US13274		19960816	
			19980728	PCT 371 date
			19980728	PCT 102(e) date

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Ware, T.
LEGAL REPRESENTATIVE: Titus, Robert D.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 1105
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The availability of serotonin, norepinephrine and dopamine in the brain is increased by administering a serotonin reuptake inhibitor with a serotonin 1A antagonist and L-tryptophan or 5-hydroxy-L-tryptophan.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . need thereof in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1## R.sub.1 is an optional methyl group substituted on one. . .

SUMM **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)-indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "**pindolol**" in this document.

SUMM fluoxetine/**pindolol**/5-hydroxy-L-tryptophan

SUMM duloxetine/**pindolol**/5-hydroxy-L-tryptophan

SUMM **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .

SUMM . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .

SUMM . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

SUMM . . . compound may be combined in a single dosage form with the other chosen compounds. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . component. Still further, a suspension may be prepared in which the first and third components are present as solution or **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

SUMM **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric**

pellets.

SUMM A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

10 mg Duloxetine base/capsule
Bill of Materials

Beads	
Sucrose - starch nonpareils, 20-25 mesh	60.28 mg
Duloxetine layer	
Duloxetine	11.21
Hydroxypropylmethylcellulose	3.74
Separating layer	
Hydroxypropylmethylcellulose	2.51
Sucrose	5.00
Talc, 500 mesh	10.03
Enteric layer	
HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
Triethyl citrate	5.00
Talc, 500 mesh	7.52
Finishing layer	
Hydroxypropylmethylcellulose	8.44
Titanium dioxide	2.81
Talc	Trace
	141.60 mg

DETD . . . bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The **separating** layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

DETD In order to prepare the **enteric** coating suspension, purified water was cooled to 10.degree. C. and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the **HPMCAS** and talc were added and agitated until homogeneity was obtained, and the **HPMCAS** was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The **enteric** suspension was maintained at 20.degree. C. during the coating process. The **enteric** suspension was then added to the partially completed **pellets** in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50.degree. C. The product was dried in the Wurster at 50.degree. C. when the **enteric** suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60.degree. C.. . . . layer was then applied which consisted of a 4.5% w/w/hydroxypropylmethylcellulose solution containing titanium dioxide and propylene glycol as plasticizer. The **pellets** were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

DETD

	Quantity

(mg/capsule)

Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
5-Hydroxy-L-tryptophan	50	
Starch, dried	150	
Magnesium stearate	10	
Total	260	mg

DETD

	Weight
(+)-Duloxetine, hydrochloride	10
Pindolol	10
L-Tryptophan	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	60.00
Total	115.75

DETD . . . is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The **granules** so produced are dried at 50.degree. C. and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the **granules** which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

DETD In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate, (-)-**pindolol**, and L-tryptophan. The rats were prepared as described above, and L-tryptophan administered intraperitoneally at 100 mg/kg, 150 minutes after the start of the experiment. **Pindolol** was administered subcutaneously at 5 mg/kg, at 270 minutes after the start of the experiment. A mixture of fluoxetine (10 mg/kg) and **pindolol** (10 mg/kg) was administered intraperitoneally at 390 minutes after the start of the experiment. L-Tryptophan was administered intraperitoneally at 100. . .

DETD Administration of a mixture of fluoxetine and **pindolol** at 390 minutes followed by the administration of tryptophan 30 minutes later resulted in a remarkable increase in serotonin concentration to nearly 800% of basal levels. The administration of fluoxetine and **pindolol** alone has been reported to increase serotonin levels to 400% of basal levels (Dreshfield, et al., Neurochemical Research, 21(5), 557-562. . .

DETD In this test, the combination therapy comprised fluoxetine as the hydrochloride of the racemate, **pindolol** as the racemate, and L-tryptophan. **Pindolol** was continuously infused subcutaneously at a rate of 50 mg/kg/hr beginning at 120 minutes after the beginning of the experiment.. . .

CLM What is claimed is:

. . . need thereof in combination with a second component selected from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR4## R.sub.1 is an optional methyl group substituted on one. . .

. . . and duloxetine in combination with a second component selected from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR7## R.sub.1 is an optional methyl group substituted on one. . .

13. A composition of claim 8 wherein the second component compound is

pindolol, penbutolol, propranolol, tertatolol or 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

14. A composition of claim 12 wherein the second component compound is **pindolol**, penbutolol, propranolol, tertatolol or 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

IT 73-22-3, Tryptophan, biological studies 525-66-6, Propranolol 749-02-0, Spiperone 4350-09-8, 5-Hydroxy-L-tryptophan 13523-86-9, Pindolol 13655-52-2, Alprenolol 38363-40-5, Penbutolol 54739-18-3, Fluvoxamine **54910-89-3**, Fluoxetine 56296-78-7, Fluoxetine hydrochloride 59729-33-8, Citalopram 61869-08-7, Paroxetine 79617-96-2, Sertraline 83688-84-0, Tertatolol 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 116539-59-4, Duloxetine 127414-58-8 133025-23-7, WAY 100135 135308-68-8, (S)-UH-301 136434-34-9 146714-97-8, WAY 100635
(potentiation of serotonin response)

L11 ANSWER 3 OF 8 USPATFULL

ACCESSION NUMBER:	1999:65077 USPATFULL
TITLE:	Fluoxetine **enteric pellets** and methods for their preparation and use
INVENTOR(S):	Anderson, Neil R., West Lafayette, IN, United States Harrison, Roger G., Zionsville, IN, United States Lynch, Daniel F., Indanapolis, IN, United States Oren, Peter L., Fishers, IN, United States
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

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ASSISTANT EXAMINER:	Seidleck, Brian K.
LEGAL REPRESENTATIVE:	Titus, Robert D., Conrad, Robert A.
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A superior **enteric** formulation of the antidepressant drug, fluoxetine, is in the form of **enteric pellets** of which the **enteric** layer comprises hydroxypropylmethylcellulose acetate succinate.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Fluoxetine **enteric pellets** and methods for their preparation and use

AB A superior **enteric** formulation of the antidepressant drug, fluoxetine, is in the form of **enteric pellets** of which the **enteric** layer comprises hydroxypropylmethylcellulose acetate succinate.

SUMM This invention belongs to the field of pharmaceutical science, and provides a superior **enteric** formulation of the anti-depressant drug, fluoxetine.

SUMM **Enteric** pharmaceutical formulations are manufactured in such a way that the product passes unchanged through the stomach of the patient, and. . . ingredient is in the inner part of the tablet or pellet and is enclosed in a film or envelope, the "**enteric** coating", which is insoluble in acid environments, such as the stomach, but is soluble in near-neutral environments such as the. . .

SUMM Certain difficulties arose in preparing conventional **enteric** formulations of fluoxetine. In particular, fluoxetine was found to react with many **enteric coatings** to form a slowly--or even insoluble coating. Similar reactions with **enteric coatings** have been observed with other drugs--duloxetine, nortriptyline, desipramine, sertraline and paroxetine.

SUMM Duloxetine, undergoing clinical evaluation as a candidate antidepressant, is (+)-N-methyl-3-(1-naphthalenyloxy)-2-thiophenepropanamine, and is commonly used as its hydrochloride salt. An **enteric** coated formulation of duloxetine is claimed in U.S. Pat. No. 5,508,276, to avoid acid degradation of the compound in the. . .

SUMM The present invention was created through efforts to solve the above and other problems, and provides a superior **enteric** formulation of fluoxetine.

SUMM The present invention provides an **enteric** fluoxetine pellet comprising a) a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropyl-methylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer.

SUMM The invention also provides a method of manufacturing an **enteric** fluoxetine pellet comprising a) providing a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) optionally, applying to the core a **separating** layer comprising one or more pharmaceutically acceptable excipients; c) applying an **enteric** layer comprising **HPMCAS** and one or more pharmaceutically acceptable excipients, wherein the **HPMCAS** is applied as an aqueous solution or suspension and the application takes place in an apparatus of the fluid bed. . .

SUMM . . . of percentage, ratio, proportion and the like, will be in weight units unless otherwise stated. Expressions of proportions of the **enteric** product will refer to the product in dried form, after the removal of the water in which many of the. . .

SUMM The various components and **layers** of the pellet will be individually discussed as follows, together with the methods of adding the different ingredients to build. . .

SUMM The size of the cores depends, of course, on the desired size of the pellet to be manufactured. In general, **pellets** can be as small as 0.1 mm, or as large as 2 mm. Preferred cores are from about 0.3 to about 0.8 mm, in order to provide finished **pellets** in the desired preferred size range of from about 0.5 to about 1.5 mm in diameter.

SUMM . . . the cores to be of a reasonably narrow particle size distribution, in order to improve the uniformity of the various **coatings** to be added and the homogeneity of the final product. For example, the cores may be specified as being of. . .

SUMM The amount of cores to be used obviously depends on the weights and thicknesses of the added **layers**; in general, the cores comprise from about 10 to about 70 percent of the product. More preferably, the charge of. . .

SUMM . . . in general. The amount of fluoxetine, of course, depends on the desired dose of the drug and the quantity of **pellets** which it is desired to administer. The dose of fluoxetine is in the range of 20-100 mg (base equivalent), more usually 80-90 mg, and the usual amount of **pellets** is that amount which is conveniently held in gelatin capsules. Comparison of the volume of gelatin capsules and the desired. . .

SUMM . . . conducted in conventional coating pans similar to those employed in sugar coating processes. This process can be used to prepare **pellets**, but this equipment has less efficient air flow and drying capabilities which limits application rates and can result in longer. . .

SUMM . . . plate equipment typically consists of a cylinder, the bottom of

which is a rotatable plate. Motion of the mass of **particles** to be coated is provided by friction of the mass between the stationary wall of the cylinder and the rotating. . .

SUMM When a powder coating is to be applied, the mass of **pellets**, in the present case, is maintained in a sticky state, and the powder to be adhered to them, fluoxetine in this case, is added continuously or periodically and adheres to the sticky **pellets**. When all of the fluoxetine has been applied, the spray is stopped and the mass is allowed to dry in. . .

SUMM . . . spraying nozzle close above the bottom, or a downward-spraying nozzle mounted above the product mass. The cylinder is charged with **particles** to be coated, sufficient volume of air is drawn through the bottom of the cylinder to suspend the mass of **particles**, and the liquid to be applied is sprayed onto the mass. The temperature of the fluidizing air is balanced against the spray rate to maintain the mass of **pellets** or tablets at the desired level of moisture and stickiness while the coating is built up.

SUMM . . . a mass of pharmaceutical excipients, moistening the mass with water or a solvent, drying, and breaking the mass into sized **particles** in the same size range as described above for the inert cores. This can be accomplished via the process of. . .

SUMM **Separating** Layer

SUMM The **separating** layer between the fluoxetine-containing core and the **enteric** layer is not required, but is a preferred feature of the formulation. The functions of the **separating** layer, if required, are to provide a smooth base for the application of the **enteric** layer, to prolong the pellet's resistance to acid conditions, and to improve stability by inhibiting any interaction between the drug and the **enteric** polymer in the **enteric** layer.

SUMM The smoothing function of the **separating** layer is purely mechanical, the objective of which is to improve the coverage of the **enteric** layer and to avoid thin spots in it, caused by bumps and irregularities on the core. Accordingly, the more smooth and free of irregularities the core can be made, the less material is needed in the **separating** layer, and the need for the smoothing characteristic of the **separating** layer may be avoided entirely when the fluoxetine is of extremely fine particle size and the core is made as. . .

SUMM It has been found that, when a pharmaceutically acceptable non-reducing sugar is added to the **separating** layer, the pellet's resistance to acid conditions is markedly and surprisingly increased. Accordingly, such a sugar may be included in the **separating** layer applied to the cores, either as a powdered mixture, or dissolved as part of the sprayed-on liquid. A sugar-containing **separating** layer can reduce the quantity of **enteric** polymer required to obtain a given level of acid resistance. It therefore considerably reduces the expense of the present formulated product. Use of less **enteric** polymer reduces both the materials cost and processing time, and also reduces the amount of polymer available to react with fluoxetine. The inhibition of any core/**enteric** layer interaction is mechanical. The **separating** layer physically keeps the components in the core and **enteric layers** from coming into direct contact with each other. In some cases, the **separating** layer can also act as a diffusional barrier to migrating core or **enteric** layer components dissolved in product moisture. The **separating** layer can also be used as a light barrier by opacifying it with agents such as titanium dioxide, iron oxides. . .

SUMM In general, the **separating** layer is composed of coherent or polymeric materials, and finely powdered solid excipients which constitute fillers. When a sugar is used in the **separating** layer, it is applied in the form of an aqueous solution and constitutes

part of or the whole of the coherent material which sticks the **separating** layer together. In addition to or instead of the sugar, a polymeric material may also be used in the **separating** layer. For example, substances such as hydroxypropylmethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like may be used in small amounts to increase the adherence and coherence of the **separating** layer.

SUMM It is further advisable to use a filler excipient in the **separating** layer to increase the smoothness and solidity of the layer. Substances such as finely powdered talc, silicon dioxide and the. . . universally accepted as pharmaceutical excipients and may be added as is convenient in the circumstances to fill and smooth the **separating** layer.

SUMM In general, the amount of sugar in the **separating** layer may be in the range of from about 2% to about 10% of the product, when a sugar is. . .

SUMM The **separating** layer may be applied by spraying aqueous solutions of the sugar or polymeric material, and dusting in the filler as has been described in the preparation of a fluoxetine layer. The smoothness and homogeneity of the **separating** layer can be improved, however, if the filler is thoroughly dispersed as a suspension in the solution of sugar and/or. . . suspension is sprayed on the core and dried, using equipment as described above in the preparation of cores with fluoxetine **layers**.

SUMM **Enteric** Layer

SUMM The **enteric** layer is comprised of an **enteric** polymer, which must be chosen for compatibility with fluoxetine as discussed above. The polymer must be one having only a small number of carboxylic acid groups per unit weight or repeating unit of the polymer. The preferred **enteric** polymer is hydroxypropylmethylcellulose acetate succinate (**HPMCAS**), which product is defined as containing not less than 4% and not more than 28% of succinoyl groups, which are. . . the only free carboxylic groups in the compound. See Japanese Standards of Pharmaceutical Ingredients 1991, page 1216-21, Standard No. 19026. **HPMCAS** is available from Shin-Etsu Chemical Co., Ltd., Tokyo, Japan, under the trademark AQOAT. It is available in two particle size. . .

SUMM **Enteric** polymers may be applied as **coatings** from aqueous suspensions, from solutions in aqueous or organic solvents, or as a powder. Application from organic solvents is presently. . . difficulty in either disposing of solvent vapors or recovering the evaporated solvent. Accordingly, no detailed discussion of application of the **enteric** layer from organic solvents will be given here, but the pharmaceutical scientist will recognize that such application is entirely possible. . .

SUMM The **enteric** polymer can also be applied according to a method described by Shin-Etsu Chemical Co. Ltd. (Obara, et al., Poster PT6115, AAPS Annual Meeting, Seattle, Wash., Oct. 27-31, 1996). When the **enteric** polymer is applied as a powder the **enteric** polymer is added directly in the solid state to the tablets or **pellets** while plasticizer is sprayed onto the tablets or **pellets** simultaneously. The deposit of solid **enteric** **particles** is then turned into a film by curing. The curing is done by spraying the coated tablets or **pellets** with a small amount of water and then heating the tablets or **pellets** for a short time. This method of **enteric** coating application can be performed employing the same type of equipment as described above in the preparation of cores with fluoxetine **layers**

SUMM When the **enteric** polymer is applied as an aqueous suspension, a problem in obtaining a uniform, coherent film often results. It is very advisable, accordingly, to purchase a fine particle grade or grind the **particles** of polymer to an extremely small size before application. It is possible either to grind the dry polymer, as in. .

. form. Slurry grinding is generally preferable, particularly since it can be used also to grind the filler portion of the **enteric** layer in the same step. It is advisable to reduce the average particle size of the **enteric** polymer to the range from about 1 .mu.m to about 5 .mu.m, preferably no larger than 3 .mu.m.

SUMM When the **enteric** polymer is applied in the form of a suspension, it is important to assure that the suspension remains homogeneous, and. . . taken to assure that the suspension is kept moving briskly through the equipment to cool the tubing and nozzle. When **HPMCAS** is used, in particular, it is advisable to cool the suspension below 20.degree. C. before application, to cool the tubing. . .

SUMM It is preferred in the present invention, however, to apply the **enteric** polymer as an aqueous solution whenever it is possible to do so. In the case of **HPMCAS**, dissolution of the polymer can be obtained by neutralizing the polymer, preferably with ammonia. Neutralization of the polymer may be. . . the polymer when such a process is to be used. Use of neutralized polymer more readily provides a smooth, coherent **enteric** layer than when a suspended polymer is used, and use of partially neutralized polymer provides intermediate degrees of smoothness and coherency. Particularly when the **enteric** layer is applied over a very smooth **separating** layer, excellent results may be obtained from partially neutralized **enteric** polymer.

SUMM . . . Still another preferred manner of neutralization is from about 25% to about 65% neutralized. It is found, however, that the **enteric** polymer in the resulting product, after drying, is neutralized to a lesser extent than when applied. When neutralized or partially neutralized **HPMCAS** is applied, the **HPMCAS** in the final product is from about 0% to about 25% neutralized, more preferably from about 0% to about 15%. . .

SUMM Most **enteric** polymers require the addition of a plasticizer for best results. In the case of **HPMCAS**, the preferred plasticizer is triethyl citrate, used in an amount up to about 15%-30% of the amount of **enteric** polymer in aqueous suspension application. When a neutralized **HPMCAS** is employed, lower levels or no plasticizer may be required.

SUMM Usually, an **enteric** layer is filled with a powdered excipient such as talc, glyceryl monostearate or hydrated silicon dioxide to build up the. . . solids in the range of from about 1% to about 10% of the final product may be added to the **enteric** polymer mixture, while the amount of **enteric** polymer itself is usually in the range from about 5% to about 25%, more preferably, from about 10% to about. . .

SUMM Application of the **enteric** layer to the **pellets** follows the same general procedure previously discussed, using fluid bed type equipment with simultaneous spraying of **enteric** polymer solution or suspension and warm air drying. Temperature of the drying air and the temperature of the circulating mass of **pellets** should be kept in the ranges advised by the manufacturer of the **enteric** polymer.

SUMM A finishing layer over the **enteric** layer is not necessary in every case, but frequently improves the elegance of the product and its handling, storage and. . . less than 1% of an anti-static ingredient such as talc or silicon dioxide, simply dusted on the surface of the **pellets**. Another simple finishing layer is a small amount, about 1%, of a wax such as beeswax melted onto the circulating mass of **pellets** to further smooth the **pellets**, reduce static charge, prevent any tendency for **pellets** to stick together, and increase the hydrophobicity of the surface.

SUMM More complex finishing **layers** may constitute a final sprayed-on layer of ingredients. For example, a thin layer of polymeric material such as hydroxypropylmethylcellulose, polyvinylpyrrolidone. .

. color agent such as red or yellow iron oxide. Such a layer quickly dissolves away in the stomach, leaving the **enteric** layer to protect the fluoxetine, but provides an added measure of pharmaceutical elegance and protection from mechanical damage to the. . .

SUMM Finishing **layers** to be applied to the present product are of essentially the same types commonly used in pharmaceutical science to smooth, seal and color **enteric** products, and may be formulated and applied in the usual manners.

DETD The following Examples set out the preparation of a number of different **enteric granules** within the concept of the present invention. The Examples are intended further to enlighten the reader about the present **enteric pellets** and their methods of manufacture; additional variations within the concept of the invention will be clear to the pharmaceutical scientist. . .

DETD . . . will be expressed in terms of the amount of each ingredient used to prepare a single unit dose of the **granules**. Following the bill of materials, the process will be described, giving the equipment and the batch size used in the. . .

DETD

Bill of Materials

Cores	
Sucrose-starch nonpareils, 30-35 mesh	134.15 mg
Fluoxetine layer	
Fluoxetine	100.58 mg
Sucrose	25.72 mg
Hydroxypropylmethylcellulose	12.89 mg
Separating layer	
Hydroxypropylmethylcellulose	9.45 mg
Sucrose	28.24 mg
Talc, 500 mesh	50.21 mg
Enteric layer	
HPMCAS-LF	65.66 mg
Triethyl citrate	13.14 mg
Talc, 500 mesh	19.66 mg
Finishing Layer	
Color mixture white (HPMC + titanium dioxide)	43.02 mg
HPMC	10.78 mg
Talc. . .	

DETD . . . fitted with a Wurster column. Upon completing the application of the desired quantity of fluoxetine hydrochloride suspension, the fluoxetine core **pellets** were completely dried in the fluid bed dryer.

DETD The **separating** layer which consisted of talc 12% w/w, sucrose 6.75% w/w and hydroxypropyl methylcellulose 2.25% w/w was then applied as an aqueous suspension to the fluoxetine core **pellets**. Upon completing the application of the desired quantity of suspension, the **pellets** were completely dried in the fluid bed dryer.

DETD The **enteric** coating aqueous suspension consisted of hydroxypropyl methylcellulose acetate succinate type LF 6% w/w, talc 1.8% w/w, triethyl citrate 1.2% w/w which was fully neutralized by the addition of 0.47% w/w ammonium hydroxide. This **enteric** coating suspension was applied to the fluoxetine separation layer coated **pellets**. Upon completing the application of the desired quantity of **enteric** coating suspension, the **pellets** were completely dried in the fluid bed dryer and a small quantity of talc was added to reduce static charge.

DETD . . . 8% w/w and hydroxypropyl methylcellulose 2% w/w. Upon completing the application of the desired quantity of color coating

suspension, the **pellets** were completely dried in the fluid bed dryer and a small quantity of talc was added to reduce static charge. The resulting **pellets** were assayed for fluoxetine content and filled into capsules to provide 90 mg of fluoxetine base.

DETD

Bill of Materials

Cores	
Sucrose-starch nonpareils, 30-35 mesh	134.19 mg
Fluoxetine layer	
Fluoxetine hydrochloride	100.62 mg
Sucrose	25.77 mg
Hydroxypropylmethylcellulose	12.89 mg
Separating layer	
Hydroxypropylmethylcellulose	6.12 mg
Sucrose	18.27 mg
Talc, 500 mesh	32.49 mg
Enteric layer	
HPMCAS-LF	74.89 mg
Triethyl citrate	14.96 mg
Talc, 500 mesh	21.77 mg
Finishing layer	
Color mixture white (HPMC + titanium dioxide)	43.02 mg
HPMC	10.78 mg
Talc. . .	

DETD

Bill of Materials

Cores	
Sucrose-starch nonpareils, 30-35 mesh	121.01 mg
Fluoxetine layer	
Fluoxetine hydrochloride	100.60 mg
Sucrose	25.75 mg
Hydroxypropylmethylcellulose	12.85 mg
Separating layer	
Hydroxypropylmethylcellulose	9.48 mg
Sucrose	28.38 mg
Talc, 500 mesh	50.45 mg
Enteric layer	
HPMCAS-LF	66.78 mg
Triethyl citrate	13.36 mg
Talc 500 mesh	20.01 mg
Finishing layer	
Color mixture white (HPMC + titanium dioxide)	44.30 mg
HPMC	11.09 mg
Talc. . .	

DETD

Bill of Materials

Cores	
Sucrose-starch nonpareils, 30-35 mesh	100-150 mg
Fluoxetine layer	
Fluoxetine hydrochloride	100.5-100.8

		mg
Sucrose	20-30	mg
Hydroxypropylmethylcellulose	10-15	mg
Separating layer		
Hydroxypropylmethylcellulose	4-12	mg
Sucrose	15-35	mg
Talc, 500 mesh	25-60	mg
Enteric layer		
HPMCAS-LF	60-90	mg
Triethyl citrate	10-20	mg
Talc, 500 mesh	15-25	mg
Finishing layer		
Color mixture white (HPMC + titanium dioxide)	35-55	mg
HPMC	5-15	mg
Talc. . .		

DETD **Pellets** made according to the above examples, and gelatin capsules filled with various batches of such **pellets**, have been thoroughly tested in the manners usual in pharmaceutical science. Results of stability tests show that the **pellets** and capsules have sufficient storage stability to be distributed, marketed and used in the conventional pharmaceutical manner.

DETD Testing further shows that the **pellets** and capsules pass the conventional tests for **enteric** protection under conditions prevailing in the stomach. It has also been shown that the **pellets** release their load of fluoxetine acceptably quickly when exposed to conditions prevailing in the small intestine. Accordingly, the present invention has been demonstrated to solve the problems which previously were encountered in the formulation of other fluoxetine **pellets**.

DETD . . . only fluoxetine as an active ingredient, a combination product of fluoxetine, particularly as the hydrochloride salt, may be made with **pindolol** as described in European Patent Application Publication 687,472. These active ingredients are generally present in the amounts of approximately 60-120 mg of fluoxetine hydrochloride and 1 to 60 mg of **pindolol**.

CLM What is claimed is:

1. An **enteric** fluoxetine pellet comprising a) a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) an optional **separating** layer comprising a non-reducing sugar and one or more pharmaceutically acceptable excipients; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and one or more pharmaceutically acceptable excipients; d) an optional finishing layer.

2. A pellet of claim 1 wherein the **HPMCAS** is partially neutralized with ammonium ions to the degree that from about 0% to about 25% of the succinic acid. . .

3. A pellet of claim 2 wherein the **HPMCAS** is partially neutralized to the degree that from about 0% to about 15% of the succinic acid groups are neutralized.

. . .

4. A pellet of claim 1 wherein the **separating** layer is present.

7. A pellet of claim 6 wherein the **separating** layer is present.

8. A pellet of claim 7 wherein the **HPMCAS** is partially neutralized with ammonium ions to the degree that from about 0% to about

25% of the succinic acid. . .
9. A pellet of claim 4 wherein the **separating** layer comprises a pharmaceutically acceptable sugar.

11. A process for preparing an **enteric** fluoxetine pellet comprising a) providing a core consisting of fluoxetine and one or more pharmaceutically acceptable excipients; b) optionally, applying to the core a **separating** layer comprising a non-reducing sugar and one or more pharmaceutically acceptable excipients; c) applying an **enteric** layer comprising **HPMCAS** and one or more pharmaceutically acceptable excipients, wherein the **HPMCAS** is supplied as an aqueous solution or suspension and the application takes place in an apparatus of the fluid bed. . .
12. A process of claim 11 wherein the **HPMCAS** is fully or partially neutralized with ammonium ions.

13. A process of claim 12 wherein the **HPMCAS** is neutralized to the degree that from about 25% to about 100% of the succinic acid groups are neutralized.

14. A process of claim 11 wherein the **separating** layer is applied.

15. A process of claim 14 wherein the **separating** layer comprises a pharmaceutically acceptable sugar.

18. A process of claim 17 wherein the **separating** layer is applied and comprises a pharmaceutically acceptable sugar.

. . . formulation of claim 1 containing the following:

Cores		
Sucrose-starch nonpareils, 30-35 mesh	100-150	mg
Fluoxetine layer		
Fluoxetine hydrochloride	100.5-100.8	mg
Sucrose	20-30	mg
Hydroxypropylmethylcellulose	10-15	mg
Separating layer		
Hydroxypropylmethylcellulose	4-12	mg
Sucrose	15-35	mg
Talc, 500 mesh	25-60	mg
Enteric layer		
HPMCAS-LF	60-90	mg
Triethyl citrate	10-20	mg
Talc, 500 mesh	15-25	mg
Finishing layer		
Color mixture white (HPMC + titanium dioxide)	35-55	mg
HPMC	5-15	mg
Talc. . .		

29. A formulation according to claim 1 wherein the formulation additionally contains **pindolol**.

36. A method of claim 30 employing a formulation containing the following:

Cores		
Sucrose-starch nonpareils, 30-35 mesh	100-150	mg

Fluoxetine layer
Fluoxetine hydrochloride 100.5-100.8 mg
Sucrose 20-30 mg
Hydroxypropylmethylcellulose 10-15 mg
Separating layer
Hydroxypropylmethylcellulose 4-12 mg
Sucrose 15-35 mg
Talc, 500 mesh 25-60 mg
Enteric layer
HPMCAS-LF 60-90 mg
Triethyl citrate 10-20 mg
Talc, 500 mesh 15-25 mg
Finishing layer
Color mixture white (HPMC + titanium dioxide) 35-55 mg
HPMC 5-15 mg
Talc. . .

IT **54910-89-3**, Fluoxetine 56296-78-7, Fluoxetine hydrochloride
(enteric fluoxetine pellets)

L11 ANSWER 4 OF 8 USPATFULL

ACCESSION NUMBER:	1998:79206 USPATFULL
TITLE:	Treatment of sleep disorders
INVENTOR(S):	James, Steven Parker, Scotsdale, AZ, United States
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5776969		19980707	
APPLICATION INFO.:	US 1997-806729		19970227	(8)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	Granted
PRIMARY EXAMINER:	Richter, Johann
ASSISTANT EXAMINER:	Sackey, Ebenezer
LEGAL REPRESENTATIVE:	Titus, Robert D., Boone, David E.
NUMBER OF CLAIMS:	11
EXEMPLARY CLAIM:	1
LINE COUNT:	1174

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Disorders of sleep are treated with a combination of a serotonin reuptake inhibitor and a serotonin 1A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . and duloxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1## wherein Ar is ##STR2## R.sub.1 is an optional methyl. . .

SUMM **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "**pindolol**" in this document.

SUMM fluoxetine/**pindolol**

SUMM duloxetine/**pindolol**

SUMM **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .

SUMM . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .

SUMM . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

SUMM . . . may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . releasing area of second component. Still further, a suspension may be prepared in which the first component is present as **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

SUMM **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric pellets**.

SUMM A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

Bill of Materials

Beads	
Sucrose - starch nonpareils, 20-25 mesh	60.28 mg
Duloxetine layer	
Duloxetine	11.21
Hydroxypropylmethylcellulose	3.74
Separating layer	
Hydroxypropylmethylcellulose	2.51
Sucrose	5.00
Talc, 500 mesh	10.03
Enteric layer	
HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
Triethyl citrate	5.00
Talc, 500 mesh	7.52
Finishing layer	
Hydroxypropylmethylcellulose	8.44
Titanium dioxide	2.81
Talc	Trace
	141.60 mg

DETD . . . bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The **separating** layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

DETD In order to prepare the **enteric** coating suspension, purified water was cooled to 10.degree. C. and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the HMPCAS and talc were added and agitated until homogeneity was obtained, and the **HPMCAS** was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The **enteric** suspension was maintained at 20.degree. C. during the coating process. The **enteric** suspension was then added to the partially complete **pellets** in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50.degree. C. The product was dried in the Wurster at 50.degree. C. when the **enteric** suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60.degree. C.. . . . layer was then applied which consisted of a 4.5% w/w/hydroxypropylmethylcellulose solution containing titanium dioxide and propylene glycol as plasticizer. The **pellets** were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

DETD

	Quantity (mg/capsule)	
Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
Starch, dried	200	
Magnesium stearate	10	
Total	260	mg

DETD

	Weight
(+) -Duloxetine, hydrochloride	10
Pindolol	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	115.75

DETD . . . is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The **granules** so produced are dried at 50.degree. C. and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the **granules** which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

DETD In this test, the drugs were (+)-duloxetine, hydrochloride, administered at 4 mg/kg, and (-)-**pindolol**, at 5 mg/kg. The test was carried out in the same manner as Test 1, administering the (-)**pindolol** first at 120 minutes after start of experiment, and then the duloxetine together with a second dose of (-)-**pindolol** at 5 mg/kg at 210 minutes. The results are shown below as percent of baseline of the three monoamines, at. . .

CLM What is claimed is:

. . . and duloxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a

compound of the formula ##STR5## wherein Ar is ##STR6## R.sub.1 is an optional methyl. . .

. . . 5. A method of any one of claims 1-4 wherein the second component is chosen from the group consisting of **pindolol**, penbutolol, propranolol, tertatolol, and 4-(2-hydroxy-3-cyclohexylaminopropoxy)indole.

6. A method of claim 5 wherein the second component is **pindolol**.

11. A method of any one of claims 7-10 wherein the second component is **pindolol**.

IT 525-66-6, Propranolol 749-02-0, Spiperone 13523-86-9, Pindolol 13655-52-2, Alprenolol 26328-11-0, (-)-Pindolol 38363-40-5, Penbutolol 54739-18-3, Fluvoxamine **54910-89-3**, Fluoxetine 56296-78-7, Fluoxetine hydrochloride 59729-33-8, Citalopram 61869-08-7, Paroxetine 83688-84-0, Tertatolol 92623-85-3, Milnacipran 93413-69-5, Venlafaxine 116539-59-4, Duloxetine 127414-58-8 133025-23-7, WAY 100135 135308-68-8 136434-34-9 146714-97-8, WAY 100635 195874-82-9
(serotonin reuptake inhibitor-serotonin 1A receptor antagonist combination for treatment of sleep disorders)

L11 ANSWER 5 OF 8 USPATFULL
ACCESSION NUMBER: 96:80296 USPATFULL
TITLE: Potentiation of drug response
INVENTOR(S): Wong, David T., Indianapolis, IN, United States
Oguiza, Juan I., Indianapolis, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5552429		19960903
APPLICATION INFO.:	US 1995-442733		19950517 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-277460, filed on 19 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-260857, filed on 16 Jun 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Jones, Joseph A., Boone, David E.
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
LINE COUNT: 910
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The power of fluoxetine, venlafaxine, milnacipran and duloxetine to increase the availability of serotonin, norepinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . administering a first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1## wherein Ar is ##STR2## R.sub.1 is an optional methyl. . .
SUMM **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic

mixture are included in the word "**pindolol**" in this document.

SUMM fluoxetine/**pindolol**

SUMM duloxetine/**pindolol**

SUMM **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .

SUMM . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .

SUMM . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

SUMM . . . may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . releasing area of second component. Still further, a suspension may be prepared in which the first component is present as **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

SUMM **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric** **pellets**.

SUMM A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

Bill of Materials

Beads	
Sucrose - starch nonpareils, 20-25 mesh	60.28 mg
Duloxetine layer	
Duloxetine	11.21
Hydroxypropylmethylcellulose	3.74
Separating layer	
Hydroxypropylmethylcellulose	2.51
Sucrose	5.00
Talc, 500 mesh	10.03
Enteric layer	
HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05
Triethyl citrate	5.00
Talc, 500 mesh	7.52
Finishing layer	

Hydroxypropylmethylcellulose	8.44
Titanium dioxide	2.81
Talc	Trace
	141.60 mg

DETD . . . bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The **separating** layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

DETD In order to prepare the **enteric** coating suspension, purified water was cooled to 10.degree. C. and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the **HPMCAS** and talc were added and agitated until homogeneity was obtained, and the **HPMCAS** was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The **enteric** suspension was maintained at 20.degree. C. during the coating process. The **enteric** suspension was then added to the partially completed **pellets** in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50.degree. C. The product was dried in the Wurster at 50.degree. C. when the **enteric** suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60.degree. C.. . . . layer was then applied which consisted of a 4.5% w/w/hydroxypropylmethyl-cellulose solution containing titanium dioxide and propylene glycol as plasticizer. The **pellets** were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

DETD

	Quantity (mg/capsule)	
Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
Starch, dried	200	
Magnesium stearate	10	
Total	260	mg

DETD

	Weight
(+)-Duloxetine, hydrochloride	10
Pindolol	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	115.75

DETD . . . is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The **granules** so produced are dried at 50.degree. C. and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the **granules** which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

DETD In this test, the drugs were (+)-duloxetine, hydrochloride, administered at 4 mg/kg, and (-)-**pindolol**, at 5 mg/kg. The test was carried out in the same manner as Test 1, administering the (-)-**pindolol** first at 120 minutes after start of experiment, and then the duloxetine together with a second dose of (-)-**pindolol** at 5 mg/kg at 210

minutes. The results are shown below as percent of baseline of the three monoamines, at. . .

CLM What is claimed:

. . . in the brain, comprising administering fluoxetine to a patient in need thereof in combination with a second component which is **pindolol**.

. . . patient in need of such treatment a first component which is fluoxetine, in combination with a second component which is **pindolol**.

. . . 9. A pharmaceutical composition which comprises a first component which is fluoxetine in combination with a second component which is **pindolol**.

IT **54910-89-3D**, Fluoxetine, mixt. with serotonin 1A receptor antagonists 92623-85-3D, Milnacipran, mixt. with serotonin 1A receptor antagonists 93413-69-5D, Venlafaxine, mixt. with serotonin 1A receptor antagonists 116539-59-4D, Duloxetine, mixt. with serotonin 1A receptor antagonists 173478-21-2 173478-22-3 173478-23-4 173478-24-5 173478-25-6 173478-26-7
(potentiation of drug response by a serotonin 1A receptor antagonist)

L11 ANSWER 6 OF 8 USPATFULL

ACCESSION NUMBER:	96:65583 USPATFULL
TITLE:	Potentiation of drug response
INVENTOR(S):	Wong, David T., Indianapolis, IN, United States Oguiza, Juan I., Indianapolis, IN, United States
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5538992		19960723
APPLICATION INFO.:	US 1995-442734		19950517 (8)
RELATED APPLN. INFO.:	Division of Ser. No. US 1994-277460, filed on 19 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-260857, filed on 16 Jun 1994, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Raymond, Richard L.		
LEGAL REPRESENTATIVE:	Jones, Joseph A., Boone, David E.		
NUMBER OF CLAIMS:	15		
EXEMPLARY CLAIM:	1		
LINE COUNT:	996		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The power of fluoxetine, venlafaxine, milnacipran and duloxetine to increase the availability of serotonin, norepinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . administering a first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1## wherein Ar is ##STR2## R.sub.1 is an optional methyl. . .

DETD **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "**pindolol**" in this document.

DETD fluoxetine/**pindolol**

DETD duloxetine/**pindolol**

DETD **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .

DETD . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .

DETD . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

DETD . . . may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . releasing area of second component. Still further, a suspension may be prepared in which the first component is present as **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

DETD **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric pellets**.

DETD A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

10 mg Duloxetine base/capsule
Bill of Materials

Beads		
Sucrose - starch nonpareils, 20-25 mesh	60.28	mg
Duloxetine layer		
Duloxetine	11.21	
Hydroxypropylmethylcellulose	3.74	
Separating layer		
Hydroxypropylmethylcellulose	2.51	
Sucrose	5.00	
Talc, 500 mesh	10.03	
Enteric layer		
HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05	
Triethyl citrate	5.00	
Talc, 500 mesh	7.52	
Finishing layer		
Hydroxypropylmethylcellulose		

	8.44
Titanium dioxide	2.81
Talc	Trace
	141.60 mg

DETD . . . bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The **separating** layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

DETD In order to prepare the **enteric** coating suspension, purified water was cooled to 10.degree. C. and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the **HPMCAS** and talc were added and agitated until homogeneity was obtained, and the **HPMCAS** was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The **enteric** suspension was maintained at 20.degree. C. during the coating process. The **enteric** suspension was then added to the partially completed **pellets** in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50.degree. C. The product was dried in the Wurster at 50.degree. C. when the **enteric** suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60.degree. C.. . . . layer was then applied which consisted of a 4.5% w/w/hydroxypropylmethylcellulose solution containing titanium dioxide and propylene glycol as plasticizer. The **pellets** were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

DETD

	Quantity (mg/capsule)	
Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
Starch, dried	200	
magnesium stearate	10	
Total	260	mg

DETD

	Weight
(+)-Duloxetine, hydrochloride	10
Pindolol	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	115.75

DETD . . . is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The **granules** so produced are dried at 50.degree. C. and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the **granules** which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

DETD In this test, the drugs were (+)-duloxetine, hydrochloride, administered at 4 mg/kg, and (-)-**pindolol**, at 5 mg/kg. The test was carried out in the same manner as Test 1, administering the (-)-**pindolol** first at 120 minutes after start of experiment, and then the duloxetine together with a second dose of (-)-**pindolol** at 5 mg/kg at 210 minutes. The results are shown below as percent of baseline of the three

monoamines, at. . .
IT **54910-89-3D**, Fluoxetine, mixt. with serotonin 1A receptor antagonists 92623-85-3D, Milnacipran, mixt. with serotonin 1A receptor antagonists 93413-69-5D, Venlafaxine, mixt. with serotonin 1A receptor antagonists 116539-59-4D, Duloxetine, mixt. with serotonin 1A receptor antagonists 173478-21-2 173478-22-3 173478-23-4 173478-24-5 173478-25-6 173478-26-7
(potentiation of drug response by a serotonin 1A receptor antagonist)

L11 ANSWER 7 OF 8 USPATFULL
ACCESSION NUMBER: 96:58242 USPATFULL
TITLE: Potentiation of drug response
INVENTOR(S): Wong, David T., Indianapolis, IN, United States
Oguiza, Juan I., Indianapolis, IN, United States
PATENT ASSIGNEE(S): Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5532268		19960702
APPLICATION INFO.:	US 1995-442735		19950517 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-277460, filed on 19 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-260857, filed on 16 Jun 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Jones, Joseph A., Boone, David E.
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 925
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The power of fluoxetine, venlafaxine, milnacipran and duloxetine to increase the availability of serotonin, norepinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . administering a first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1## wherein Ar is ##STR2##
DETD **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "**pindolol**" in this document.
DETD fluoxetine/**pindolol**
DETD duloxetine/**pindolol**
DETD **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .
DETD . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .
DETD . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

DETD . . . may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . releasing area of second component. Still further, a suspension may be prepared in which the first component is present as **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

DETD **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric pellets**.

DETD A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

Bill of materials

Beads		
Sucrose-starch nonpareils, 20-25 mesh	60.28	mg
Duloxetine layer		
Duloxetine	11.21	
Hydroxypropylmethylcellulose	3.74	
Separating layer		
Hydroxypropylmethylcellulose	2.51	
Sucrose	5.00	
Talc, 500 mesh	10.03	
Enteric layer		
HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05	
Triethyl citrate	5.00	
Talc, 500 mesh	7.52	
Finishing layer		
Hydroxypropylmethylcellulose	8.44	
Titanium dioxide	2.81	
Talc	Trace	
	141.60	mg

DETD . . . bed dryer with a Wurster column was used to make this product, at a batch size of 1.0 kg. The **separating** layer was added from a 4% w/w solution of the hydroxypropylmethylcellulose in water, in which the sucrose was also dissolved.

DETD In order to prepare the **enteric** coating suspension, purified water was cooled to 10.degree. C. and the polysorbate, triethyl citrate and silicone emulsion were added and dispersed or dissolved. Then the **HPMCAS** and talc were added and agitated until homogeneity was obtained, and the **HPMCAS** was fully neutralized by addition of ammonium hydroxide until solution of the polymer was complete. To this

suspension, a carboxymethylcellulose aqueous solution, 0.5% w/w, was added and blended thoroughly. The **enteric** suspension was maintained at 20.degree. C. during the coating process. The **enteric** suspension was then added to the partially completed **pellets** in the Wurster column at a spray rate of about 15 ml/min, holding the temperature of the inlet air at about 50.degree. C. The product was dried in the Wurster at 50.degree. C. when the **enteric** suspension had been fully added, and then dried on trays for 3 hours in a dry house at 60.degree. C.. . . . layer was then applied which consisted of a 4.5% w/w/hydroxypropylmethylcellulose solution containing titanium dioxide and propylene glycol as plasticizer. The **pellets** were completely dried in the fluid bed dryer and then were then filled in size 3 gelatin capsules.

DETD

	Quantity (mg/capsule)	
Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
Starch, dried	200	
Magnesium stearate	10	
Total	260	mg

DETD

	Weight
(+)-Duloxetine, hydrochloride	10
Pindolol	10
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	115.75

DETD . . . is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The **granules** so produced are dried at 50.degree. C. and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the **granules** which, after mixing, are compressed on a tablet machine to yield tablets each weighing 170 mg.

DETD In this test, the drugs were (+)-duloxetine, hydrochloride, administered at 4 mg/kg, and (-)-**pindolol**, at 5 mg/kg. The test was carried out in the same manner as Test 1, administering the (-)-**pindolol** first at 120 minutes after start of experiment, and then the duloxetine together with a second dose of (-)-**pindolol** at 5 mg/kg at 210 minutes. The results are shown below as percent of baseline of the three monoamines, at. . .

IT **54910-89-3D**, Fluoxetine, mixt. with serotonin 1A receptor antagonists 92623-85-3D, Milnacipran, mixt. with serotonin 1A receptor antagonists 93413-69-5D, Venlafaxine, mixt. with serotonin 1A receptor antagonists 116539-59-4D, Duloxetine, mixt. with serotonin 1A receptor antagonists 173478-21-2 173478-22-3 173478-23-4 173478-24-5 173478-25-6 173478-26-7
(potentiation of drug response by a serotonin 1A receptor antagonist)

L11 ANSWER 8 OF 8 USPATFULL

ACCESSION NUMBER:	96:58218 USPATFULL
TITLE:	Potentiation of drug response
INVENTOR(S):	Wong, David T., Indianapolis, IN, United States Oguiza, Juan I., Indianapolis, IN, United States
PATENT ASSIGNEE(S):	Eli Lilly and Company, Indianapolis, IN, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5532244		19960702
APPLICATION INFO.:	US 1995-442737		19950517 (8)

RELATED APPLN. INFO.: Division of Ser. No. US 1994-277460, filed on 19 Jul 1994, now abandoned which is a continuation-in-part of Ser. No. US 1994-260857, filed on 16 Jun 1994, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Raymond, Richard L.
LEGAL REPRESENTATIVE: Jones, Joseph A., Boone, David E.
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1,12
LINE COUNT: 927

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The power of fluoxetine, venlafaxine, milnacipran and duloxetine to increase the availability of serotonin, norepinephrine and dopamine, particularly serotonin, is augmented by administration in combination with a drug which is a serotonin 1A receptor antagonist.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . administering a first component in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, spiperone, **pindolol**, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula ##STR1##

SUMM **Pindolol** (4-(2-hydroxy-3-isopropylaminopropoxy)indole) was disclosed by Troxler et al., U.S. Pat. No. 3,471,515, which describes this compound as well as a beta-blocker.. . . single isomer product is desired in a given application. Both enantiomers and the racemic mixture are included in the word "**pindolol**" in this document.

SUMM fluoxetine/**pindolol**

SUMM duloxetine/**pindolol**

SUMM **Pindolol**: from about 1 to about 60 mg once-thrice/day; preferred, from about 5 to about 60 mg once-thrice/day; also preferred, from. . .

SUMM . . . class, have short lives in the body and, accordingly, provide only short periods of activity following each dose. For example, **pindolol** is routinely administered twice/day in the prior art, and it has been administered even more often. In the context of. . .

SUMM . . . may be formulated in a manner which provides a substantially constant flow of compound to the patient. To consider only **pindolol**, at least the following references teach sustained release formulations: German Patent 3632201, capsules; Swiss Patent 634990, tablets; German Patent 3237945,. . .

SUMM . . . may be combined in a single dosage form with the chosen first component compound. For example, a small tablet or **pellets** of the second component, formulated to provide constant availability of the compound, may be combined, for example in a capsule,. . . releasing area of second component. Still further, a suspension may be prepared in which the first component is present as **particles** of pure compound, and the **particles** of the second component are coated to provide sustained release in the body. In such manners, the availability of the. . .

SUMM **Enteric** formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are. . . acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate. It is preferred to formulate duloxetine and duloxetine-containing combinations as **enteric** compositions, and even more preferred to formulate them as **enteric pellets**.

DETD A preferred duloxetine **enteric** formulation is a pellet formulation comprising a) a core consisting of duloxetine and a pharmaceutically acceptable excipient; b) an optional **separating** layer; c) an **enteric** layer comprising hydroxypropylmethylcellulose acetate succinate (**HPMCAS**) and a pharmaceutically acceptable excipient; d) an optional finishing layer. The following example demonstrates the preparation of a preferred such. . .

DETD

Bill of Materials

Beads		
Sucrose -- starch nonpareils, 20-25 mesh	60.28	mg
Duloxetine layer		
Duloxetine	11.21	
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Talc, 500 mesh	10.03	
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HPMCAS, LF grade, Shin-Etsu Chemical Co., Tokyo, Japan	25.05	
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Talc, 500 mesh	7.52	
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DETD

	Quantity (mg/capsule)

Fluoxetine, racemic, hydrochloride	20	mg
Pindolol	30	
Starch, dried	200	
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Total	260	mg

DETD

	Weight
(+)-Duloxetine, hydrochloride	10
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Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	115.75

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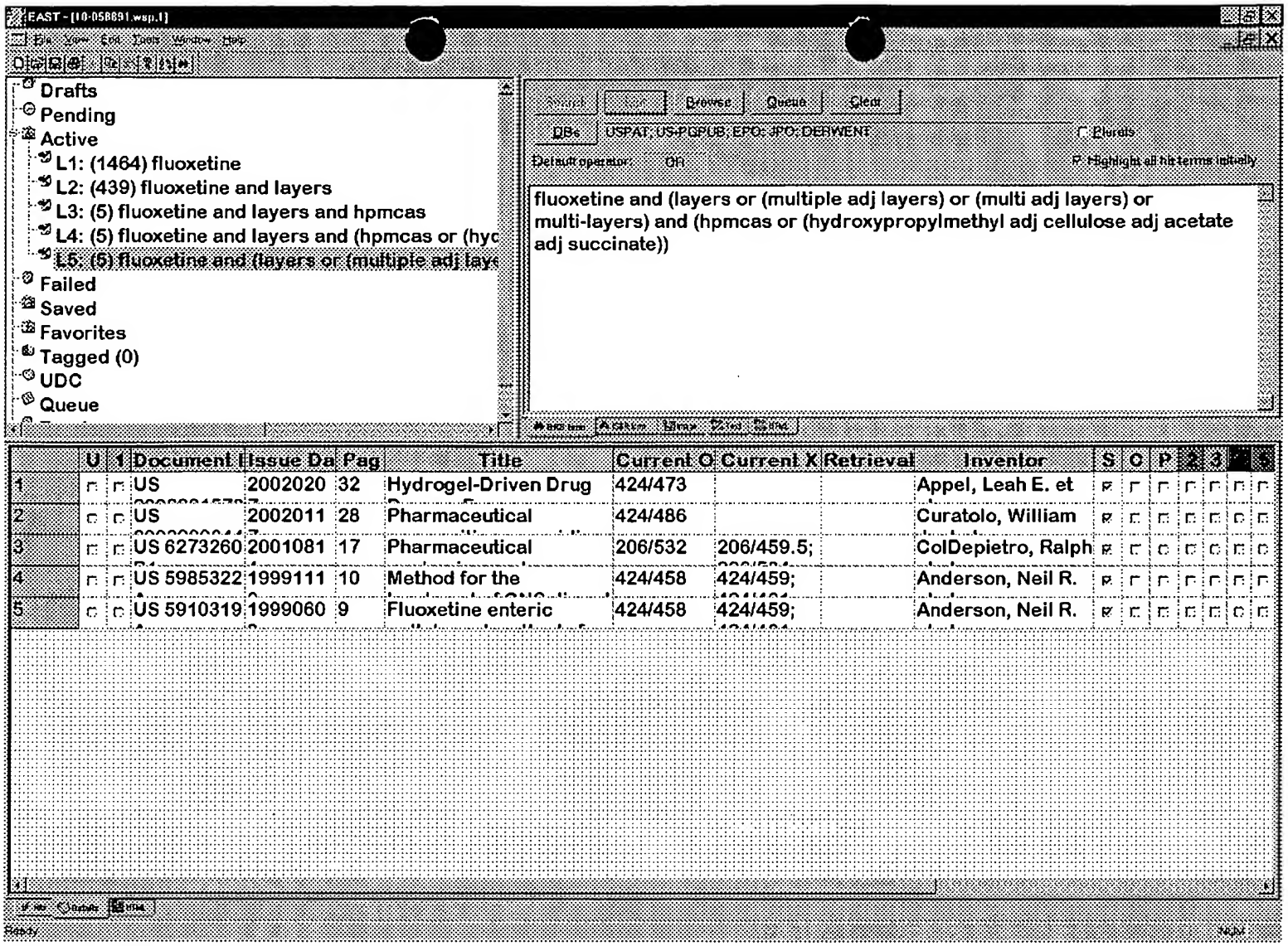
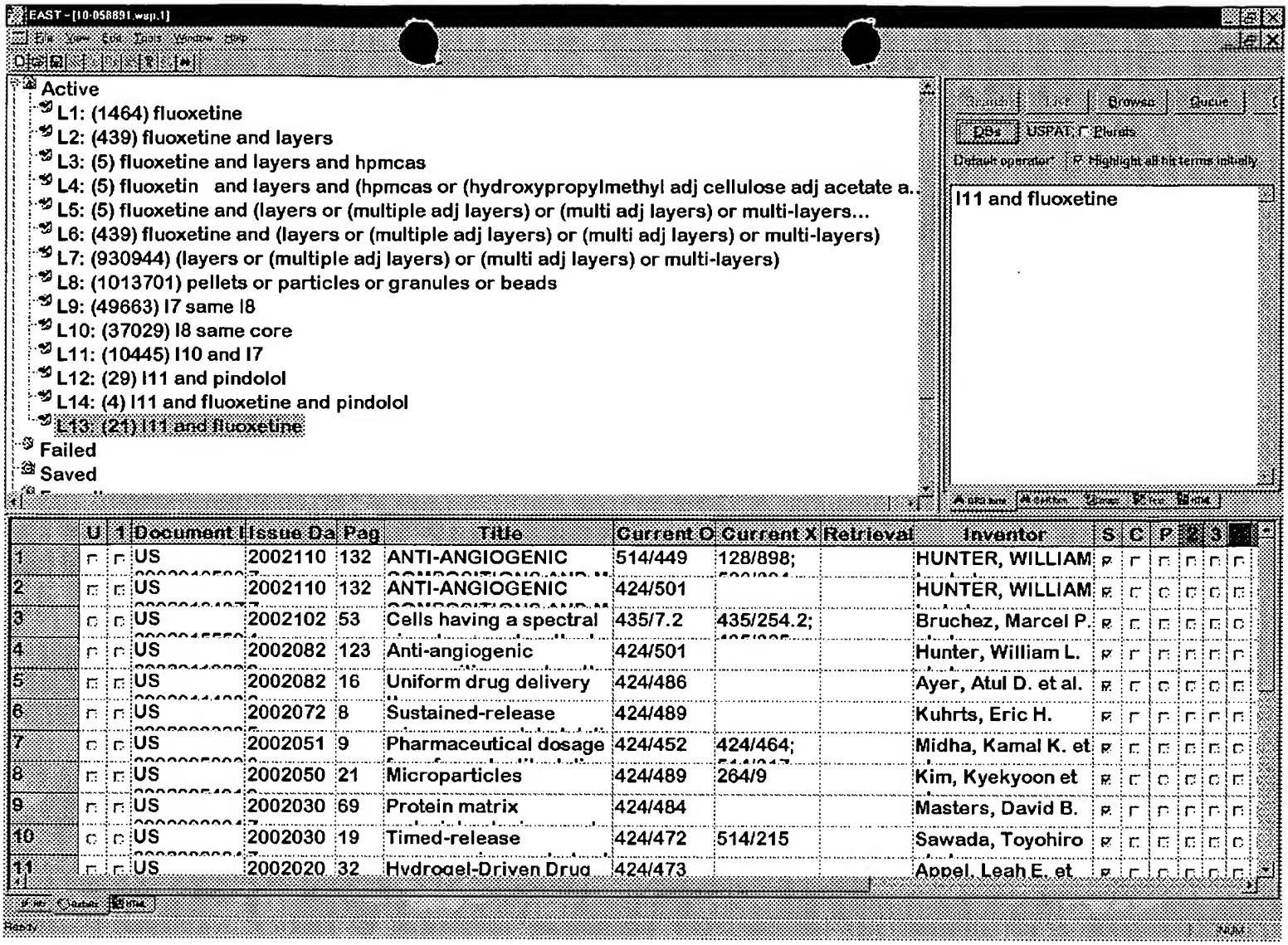
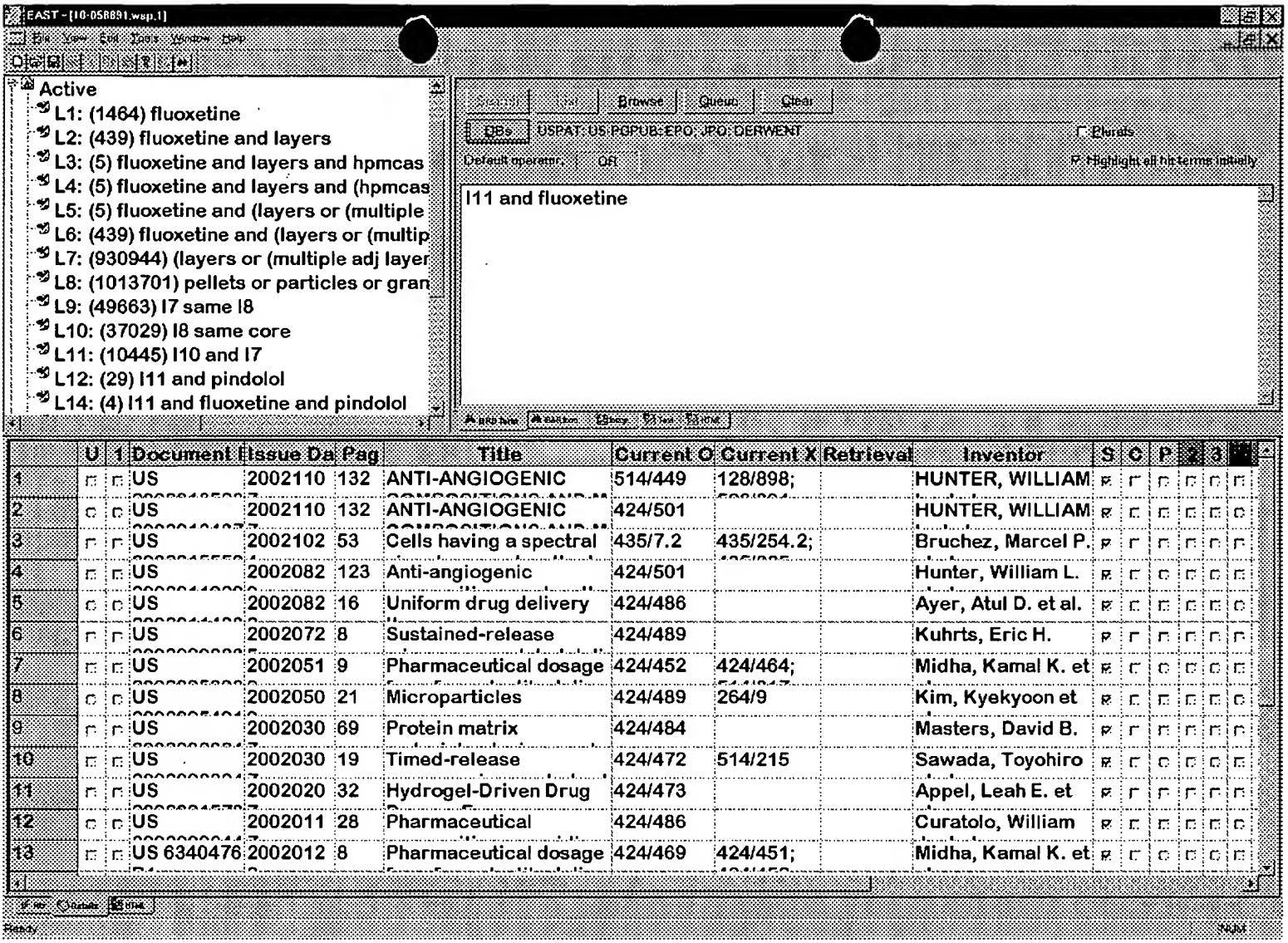
IT **54910-89-3D**, Fluoxetine, mixt. with serotonin 1A receptor antagonists 92623-85-3D, Milnacipran, mixt. with serotonin 1A receptor antagonists 93413-69-5D, Venlafaxine, mixt. with serotonin 1A receptor antagonists 116539-59-4D, Duloxetine, mixt. with serotonin 1A receptor antagonists 173478-21-2 173478-22-3 173478-23-4 173478-24-5 173478-25-6 173478-26-7
(potentiation of drug response by a serotonin 1A receptor antagonist)



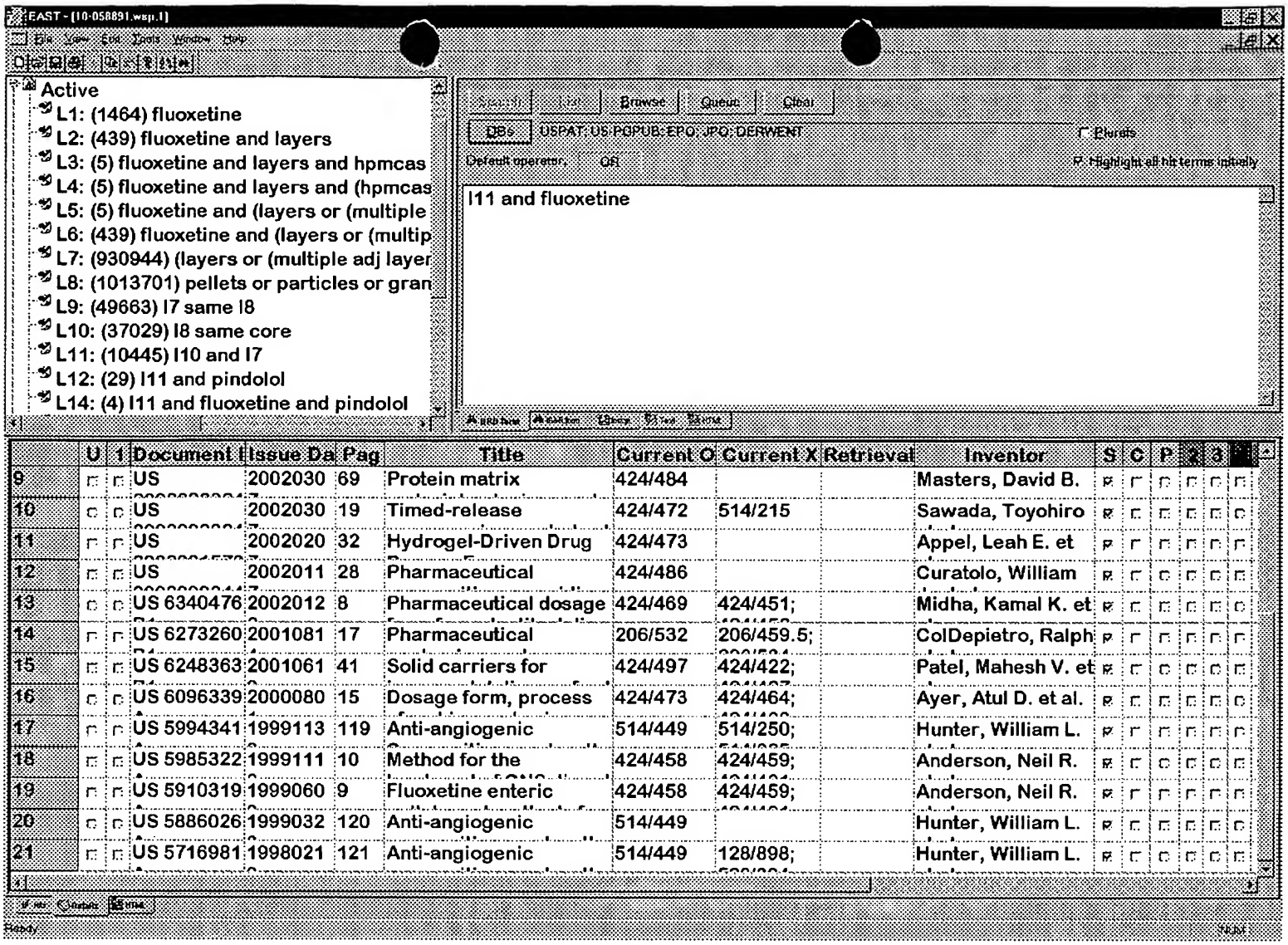
	U	1	Document I	Issue Da	Pag	Title	Current O	Current X	Retrieval	Inventor	S	O	P	2	3	4	5
1	☐	☐	US	2002020	32	Hydrogel-Driven Drug	424/473			Appel, Leah E. et	☑	☐	☐	☐	☐	☐	☐
2	☐	☐	US	2002011	28	Pharmaceutical	424/486			Curatolo, William	☑	☐	☐	☐	☐	☐	☐
3	☐	☐	US 6273260	2001081	17	Pharmaceutical	206/532	206/459.5;		ColDepietro, Ralph	☑	☐	☐	☐	☐	☐	☐
4	☐	☐	US 5985322	1999111	10	Method for the	424/458	424/459;		Anderson, Neil R.	☑	☐	☐	☐	☐	☐	☐
5	☐	☐	US 5910319	1999060	9	Fluoxetine enteric	424/458	424/459;		Anderson, Neil R.	☑	☐	☐	☐	☐	☐	☐



	U	1	Document I	Issue Da	Pag	Title	Current O	Current X	Retrieval	Inventor	S	C	P	2	3	
1	☐	☐	US	2002110	132	ANTI-ANGIOGENIC	514/449	128/898;		HUNTER, WILLIAM	☑	☐	☐	☐	☐	☐
2	☐	☐	US	2002110	132	ANTI-ANGIOGENIC	424/501			HUNTER, WILLIAM	☑	☐	☐	☐	☐	☐
3	☐	☐	US	2002102	53	Cells having a spectral	435/7.2	435/254.2;		Bruchez, Marcel P.	☑	☐	☐	☐	☐	☐
4	☐	☐	US	2002082	123	Anti-angiogenic	424/501			Hunter, William L.	☑	☐	☐	☐	☐	☐
5	☐	☐	US	2002082	16	Uniform drug delivery	424/486			Ayer, Atul D. et al.	☑	☐	☐	☐	☐	☐
6	☐	☐	US	2002072	8	Sustained-release	424/489			Kuhrts, Eric H.	☑	☐	☐	☐	☐	☐
7	☐	☐	US	2002051	9	Pharmaceutical dosage	424/452	424/464;		Midha, Kamal K. et	☑	☐	☐	☐	☐	☐
8	☐	☐	US	2002050	21	Microparticles	424/489	264/9		Kim, Kyekyoon et	☑	☐	☐	☐	☐	☐
9	☐	☐	US	2002030	69	Protein matrix	424/484			Masters, David B.	☑	☐	☐	☐	☐	☐
10	☐	☐	US	2002030	19	Timed-release	424/472	514/215		Sawada, Toyohiro	☑	☐	☐	☐	☐	☐
11	☐	☐	US	2002020	32	Hydrogel-Driven Drug	424/473			Appel, Leah E. et	☑	☐	☐	☐	☐	☐



	U	1	Document	Issue Da	Pag	Title	Current O	Current X	Retrieval	Inventor	S	C	P	2	3
1			US	2002110	132	ANTI-ANGIOGENIC	514/449	128/898;		HUNTER, WILLIAM					
2			US	2002110	132	ANTI-ANGIOGENIC	424/501			HUNTER, WILLIAM					
3			US	2002102	53	Cells having a spectral	435/7.2	435/254.2;		Bruchez, Marcel P.					
4			US	2002082	123	Anti-angiogenic	424/501			Hunter, William L.					
5			US	2002082	16	Uniform drug delivery	424/486			Ayer, Atul D. et al.					
6			US	2002072	8	Sustained-release	424/489			Kuhrts, Eric H.					
7			US	2002051	9	Pharmaceutical dosage	424/452	424/464;		Midha, Kamal K. et					
8			US	2002050	21	Microparticles	424/489	264/9		Kim, Kyekyoon et					
9			US	2002030	69	Protein matrix	424/484			Masters, David B.					
10			US	2002030	19	Timed-release	424/472	514/215		Sawada, Toyohiro					
11			US	2002020	32	Hydrogel-Driven Drug	424/473			Appel, Leah E. et					
12			US	2002011	28	Pharmaceutical	424/486			Curatolo, William					
13			US 6340476	2002012	8	Pharmaceutical dosage	424/469	424/451;		Midha, Kamal K. et					



	U	1	Document I	Issue Da	Pag	Title	Current O	Current X	Retrieval	Inventor	S	C	P	2	3
9	☐	☐	US	2002030	69	Protein matrix	424/484			Masters, David B.	☒	☐	☐	☐	☐
10	☐	☐	US	2002030	19	Timed-release	424/472	514/215		Sawada, Toyohiro	☒	☐	☐	☐	☐
11	☐	☐	US	2002020	32	Hydrogel-Driven Drug	424/473			Appel, Leah E. et	☒	☐	☐	☐	☐
12	☐	☐	US	2002011	28	Pharmaceutical	424/486			Curatolo, William	☒	☐	☐	☐	☐
13	☐	☐	US 6340476	2002012	8	Pharmaceutical dosage	424/469	424/451;		Midha, Kamal K. et	☒	☐	☐	☐	☐
14	☐	☐	US 6273260	2001081	17	Pharmaceutical	206/532	206/459.5;		ColDepietro, Ralph	☒	☐	☐	☐	☐
15	☐	☐	US 6248363	2001061	41	Solid carriers for	424/497	424/422;		Patel, Mahesh V. et	☒	☐	☐	☐	☐
16	☐	☐	US 6096339	2000080	15	Dosage form, process	424/473	424/464;		Ayer, Atul D. et al.	☒	☐	☐	☐	☐
17	☐	☐	US 5994341	1999113	119	Anti-angiogenic	514/449	514/250;		Hunter, William L.	☒	☐	☐	☐	☐
18	☐	☐	US 5985322	1999111	10	Method for the	424/458	424/459;		Anderson, Neil R.	☒	☐	☐	☐	☐
19	☐	☐	US 5910319	1999060	9	Fluoxetine enteric	424/458	424/459;		Anderson, Neil R.	☒	☐	☐	☐	☐
20	☐	☐	US 5886026	1999032	120	Anti-angiogenic	514/449			Hunter, William L.	☒	☐	☐	☐	☐
21	☐	☐	US 5716981	1998021	121	Anti-angiogenic	514/449	128/898;		Hunter, William L.	☒	☐	☐	☐	☐